Armed Forces College of Medicine

AFCM

Wrap up Biochemistry GIT Module

The active form of riboflavin is:

a) FAD
b) NAD
c) FMN
d) a & b
e) a & c

Functions of Riboflavin vitamin (B2)

Active forms: flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) which acts as hydrogen carrier *in oxidation-reduction* reactions

Reactions catalyzed by FAD

For example:

1- Succinate dehydrogenase

2- Glycine oxidase

3- Alpha keto acids dehydrogenase complex

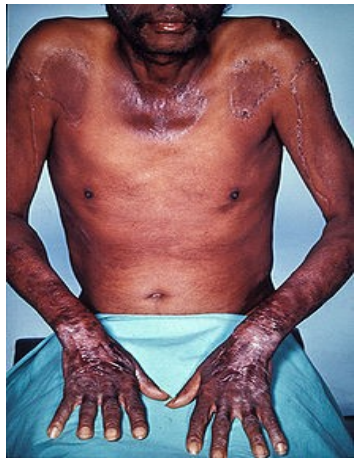
Reactions catalyzed by FMN

For example:

1- L-amino acid oxidase

2- NADH dehydrogenase complex (respiratory chain)

Case

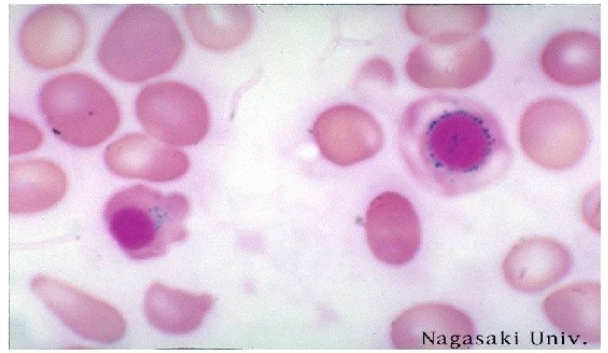


- A 45-year-old male was admitted after being found lying naked in the street talking to himself
- On admission, he had severe pallor.
- On physical examination ,his hands and forearms were covered with erythematous scaly lesions. He had persistent diarrhea without any evidence of GIT infection.
- Mental status examination on admission found that the patient was conscious but unable to answer questions correctly. Based on retrospective history from his family members, he has a history of alcohol abuse, history of seizure with no history of psychiatric disorder.

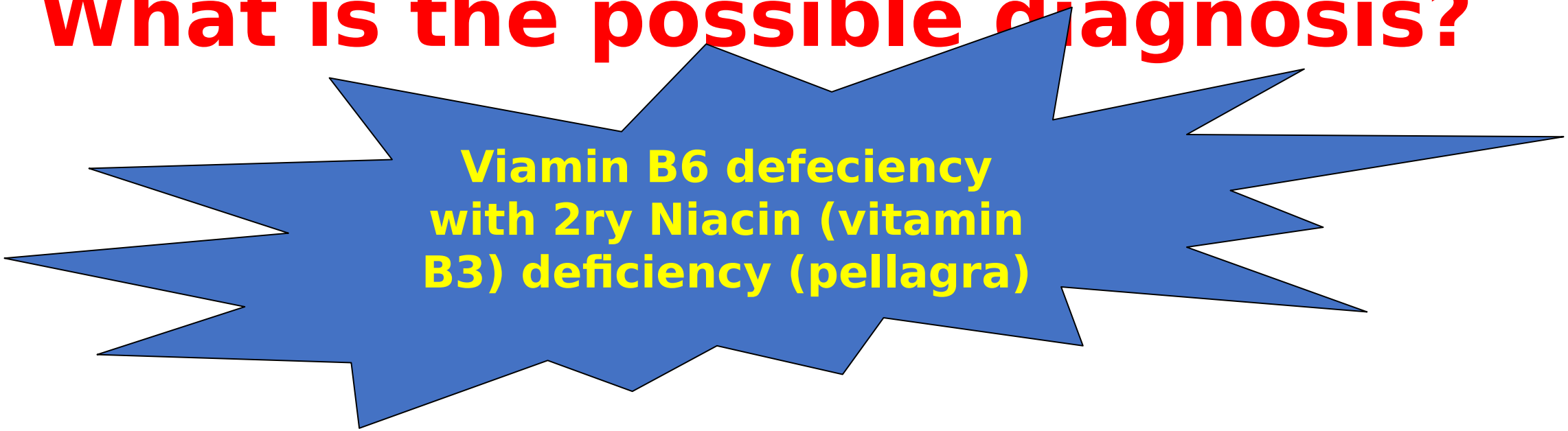
Case

- CBC revealed sideroblastic anemia with normal iron profile.
- Decreased plasma PLP level
- A 24-hour urine test found decreased levels of N-methylnicotinamide (<0.5 mg) and together with the clinical symptoms, a diagnosis of niacin deficiency (i.e., pellagra) was made.
- The patient subsequently returned to the psychiatric hospital and was treated with high-dose niacin acid, vitamins B complex. Thirty-five days after the initial admission his cognitive functioning improved, the skin color of his face and forearms lightened, the peeling of his skin lessened.

Sideroblastic Anemia



What is the possible diagnosis?

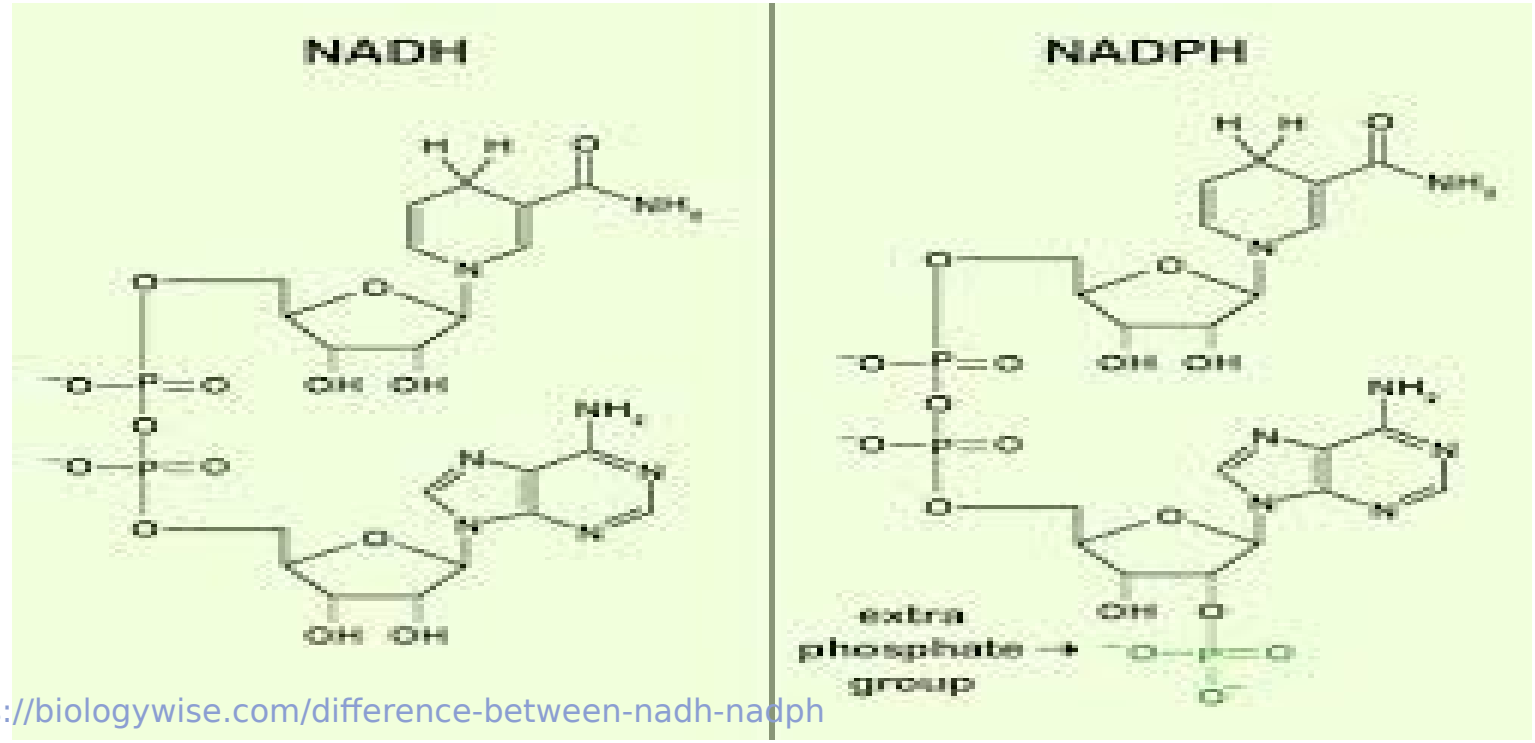


- Alcohol abuse (malnutrition, vitamin deficiency)
- Dementia
- Dermatitis in sun exposed areas
- Diarrhea

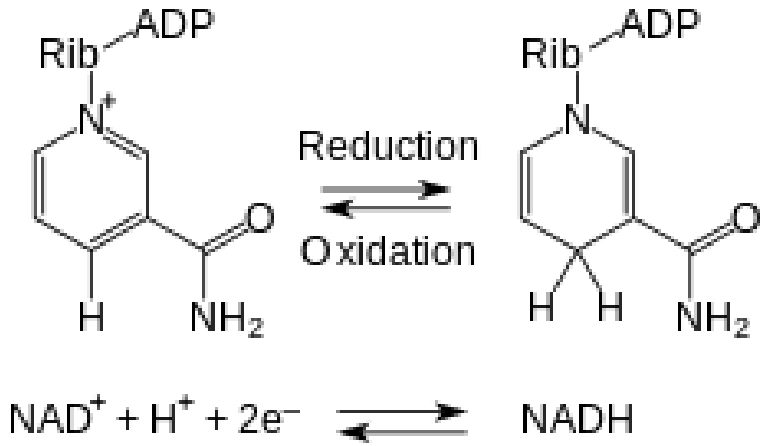
Niacin (nicotinic acid) (B_3)
Pellagra Preventive Factor (PPF)

Niacin is not strictly a vitamin since it can be synthesized from tryptophan (needs vitamin B6)

It is converted in the body into 2 hydrogen carriers (nicotinamide adenine dinucleotide **(NAD) &** nicotinamide adenine dinucleotide phosphate **(NADP)**



https://biologywise.com/difference-between-nadh-nadph



https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide

NAD dependant enzymes

1. Glyceraldehydes 3-phosphate dehydrogenase
2. Lactate dehydrogenase
3. Pyruvate dehydrogenase complex
4. Mitochondrial isocitrate dehydrogenase.

NADP dependant enzymes

HMP

1. Glucose 6–phosphate dehydrogenase
2. 6-phosphogluconate dehydrogenase
3. Malic enzyme
4. Cytosolic isocitrate dehydrogenase
5. Glutathione reductase.

NADH generated is oxidized in the respiratory chain to generate 3ATP.

Niacin Deficiency (Pellagra)

Causes:

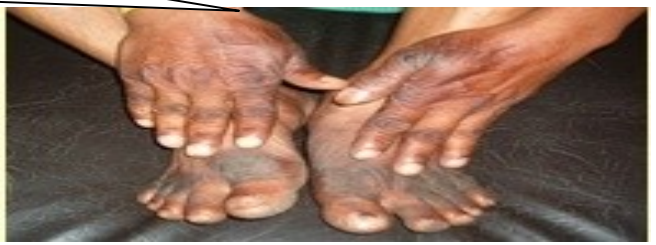
i. **Decrease Intake of Tryptophan & Niacin**

ii. **Vitamin B_6 deficiency (decreased conversion of Tryptophan to niacin)**

iii. **Caricinoid syndrome (shunting of tryptophan to serotonin synthesis)**

iv. **Hartnup's disease (decreased absorption of tryptophan): it is a Genetic condition in which there is a defect of the membrane transport mechanism for tryptophan, resulting in large losses as a result of [illegible] failure of renal reabsor[illegible]**

Explain on biochemical basis pellagra manifestations in Hartnup's disease

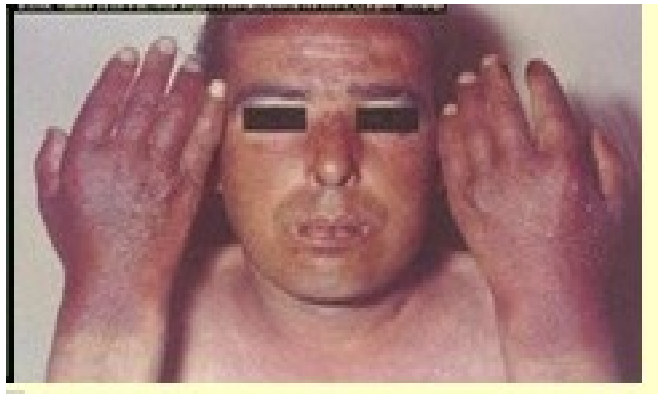


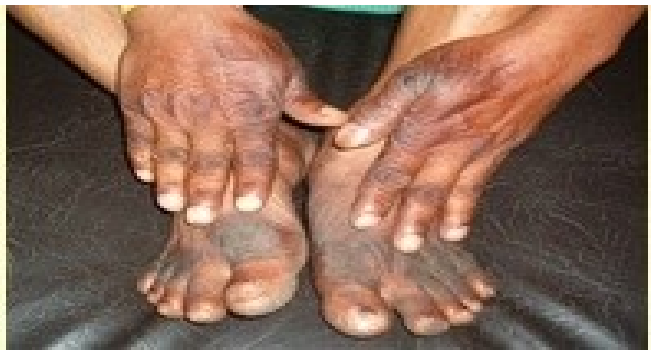
Manifestations: 3Ds

A.Dermatitis :rough scaly skin dark coloration of skin on the exposed parts of the body

B.Diarrhoea

C.Dementia: irritability, poor memory, peripheral neuritis and depression which end by dementia





Which of the following enzymes IS NOT NAD dependent?

a) glyceraldehyde 3-phosphate dehydrogenase

b) lactate dehydrogenase

c) Succinate dehydrogenase

d) pyruvate dehydrogenase complex

e) mitochondrial isocitrate dehydrogenase

Oxidation of one molecule of NADH+H yields:

a)1 ATP

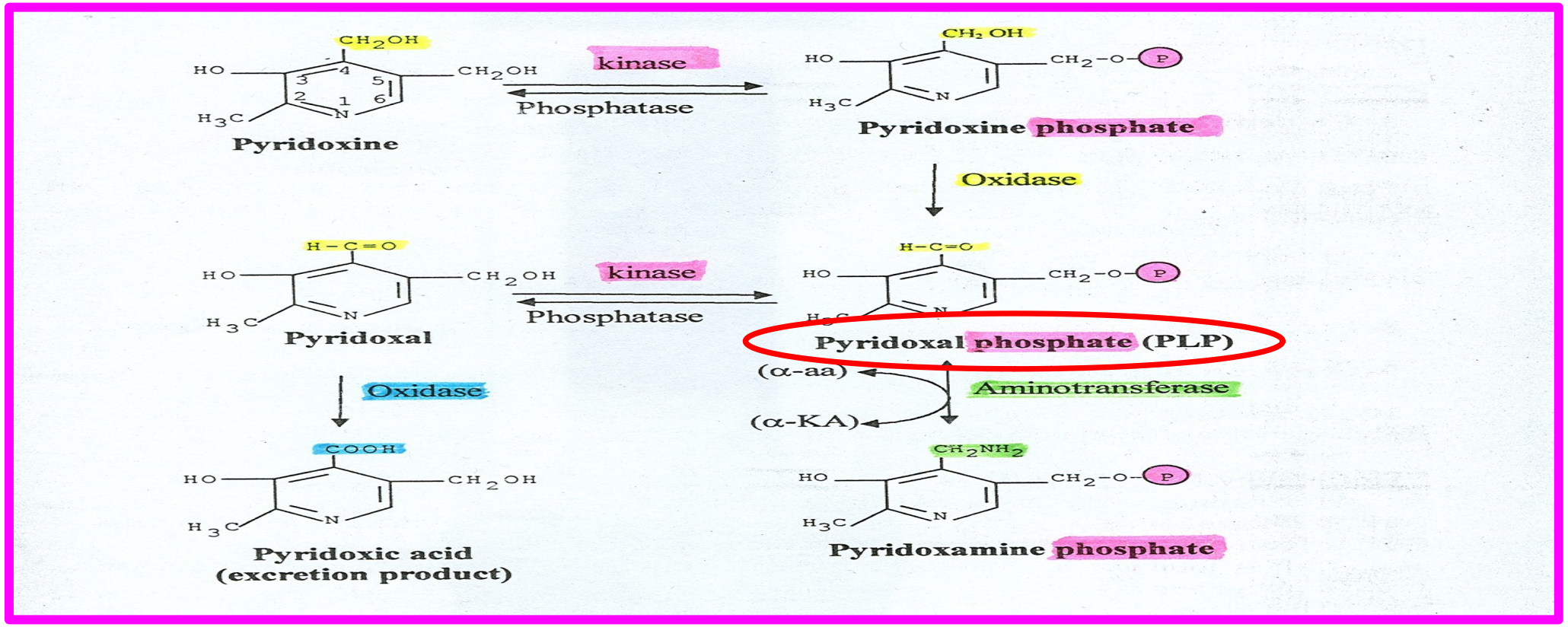
b)2 ATPs

c)3 ATPs

d)4 ATPs

Pyridoxine vitamin (B6)

- **Active form of pyridoxine is pyridoxal phosphate (PLP).**



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Functions of PLP

Protein metabolism

1 absorption of amino acids and its uptake .

2- Transamination reactions e.g. ALT and AST.

3- decarboxylation reactions of amino acids

4- Methionine and cysteine metabolism

5- conversion of tryptophan to niacin.

6-Non-oxidative deamination .

Heme synthesis

4- **ALA synthase** in heme biosynthesis. So, in B6 deficiency, anemia is common.

Lipid metabolism

6- coenzyme in the formation of **sphingosine** from palmitoyl-CoA and serine.

Carbohydrate metabolism

Muscle glycogen-7 phosphorylase has a pyridoxal phosphate at each catalytic site

Deficiency of Vitamin B_6

Causes of deficiency:

- **Pregnancy**
- **Alcoholics**
- **Oral contraceptives & Penicillamine**
- **Tuberculous patient treated with isoniazid (explained later)**

Manifestations:

1-Hypochromic anemia due to impaired heme synthesis.

2-Neurological manifestations :

I.Peripheral neuritis (stock and glove) as PLP is involved in **sphingolipid synthesis**; so B_6 deficiency leads to demyelination of nerves.

II.Convulsions, particularly in children due to decreased formation of GABA.

3-Pellagra like manifestations due to decreased conversion of tryptophan to niacin.

4-Homocysteinemia and homocystinuria

Explain on a biochemical causes neurological manifestation in vitamin B6 deficiency?

Which of the following reactions is likely to be impaired in vitamin B6 deficiency?

a)Ornithine to citrulline

b)Histidine to Histamine

c)Glutamate to glutamine

d)Propionyl coA to methylmalonyl CoA

e)Phenylalanine to tyrosine

Explain the likely cause of anemia in this patient.

vitamin B6 is required for the action of ALA synthase in heme biosynthesis. So, in B6 deficiency, anemia is common.

Enumerate decarboxylation reactions requiring vitamin B6.

i- Glutamate ———→ gamma amino butyric acid (GABA)

ii- Histidine ———→ histamine

iii-5- Hydroxytrytophan ———→ serotonin

iv- Cysteine ———→ thioethanolamine and taurine

v- Serine ———→ ethanolamine

What might be the causes of neurological manifestations in vitamin B6 deficiency?

- Peripheral neuritis as PLP is involved in sphingolipid synthesis; so B_6 deficiency leads to demyelination of nerves.
- Convulsions, due to decreased formation of GABA and other neurotransmitters.

What is the link between PLP and CHO metabolism?

PLP acts as a coenzyme for Muscle glycogen phosphorylase

Case study

A 37 -years-old female suffering from neurological manifestations is referred to a neurologist by her primary care physician.

Laboratory investigations showed low serum ceruloplasmin, and increased free copper in urine.

List Biological functions of cu enumerating enzymes that need copper as a co-factor.

- Help in iron absorption in Ferric state
- Hb synthesis
- Bone formation
- Nervous tissue function

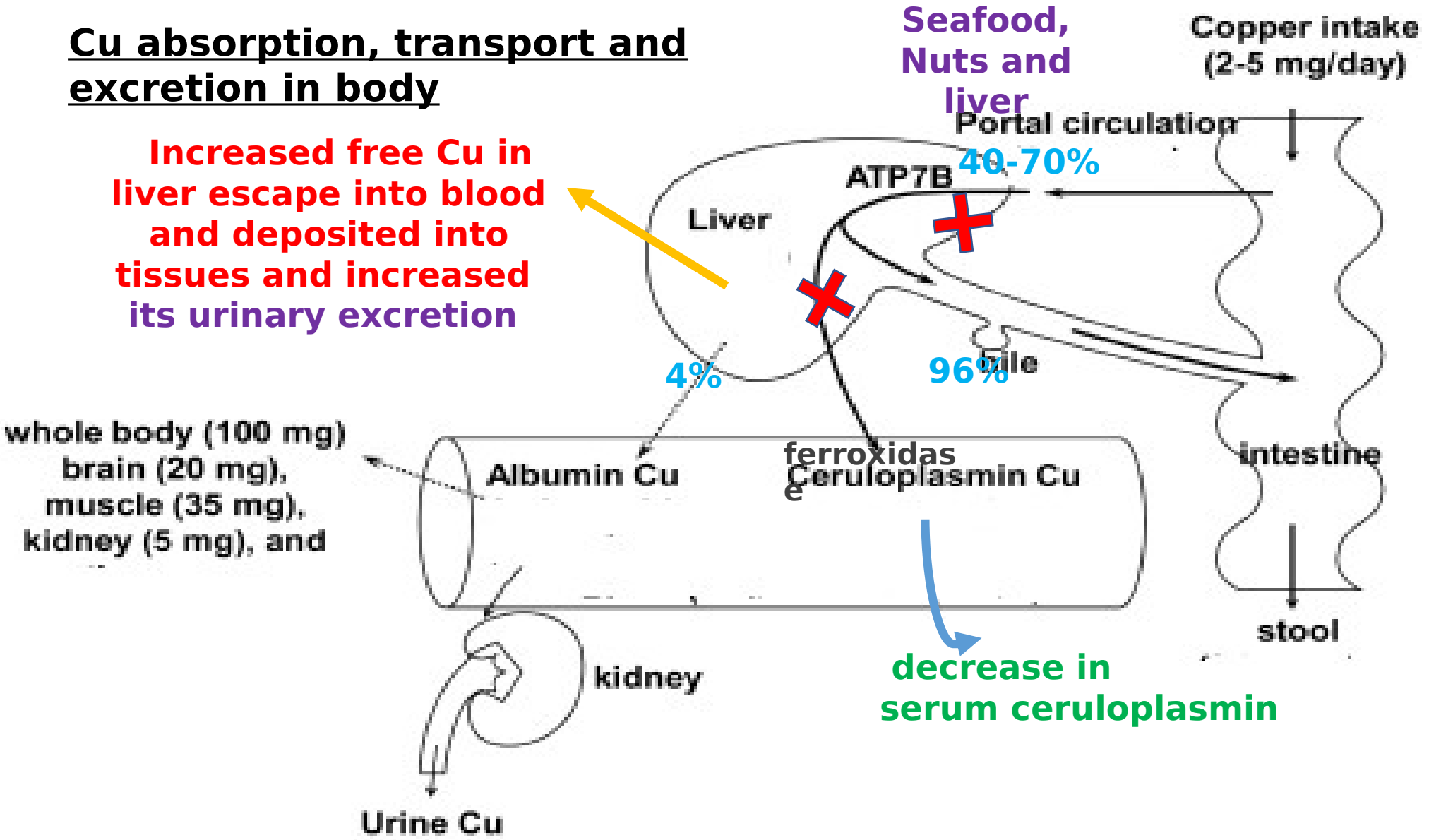
Activity of many enzymes as:

1. Superoxide Dismutase (SOD)
2. Lysayle oxidase
3. Cytochrome c oxidase
4. Monoamino oxidase
5. Ferroxidase
6. Tyrosinase
7. Dopamine b-hydroxylase
8. Peptidyl-

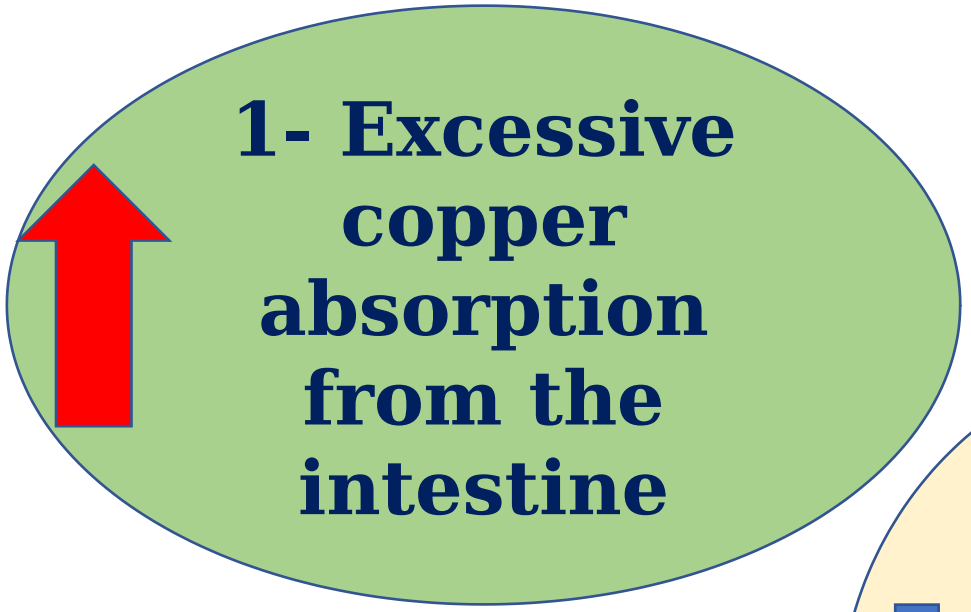
Biochemical basis of Wilson's:

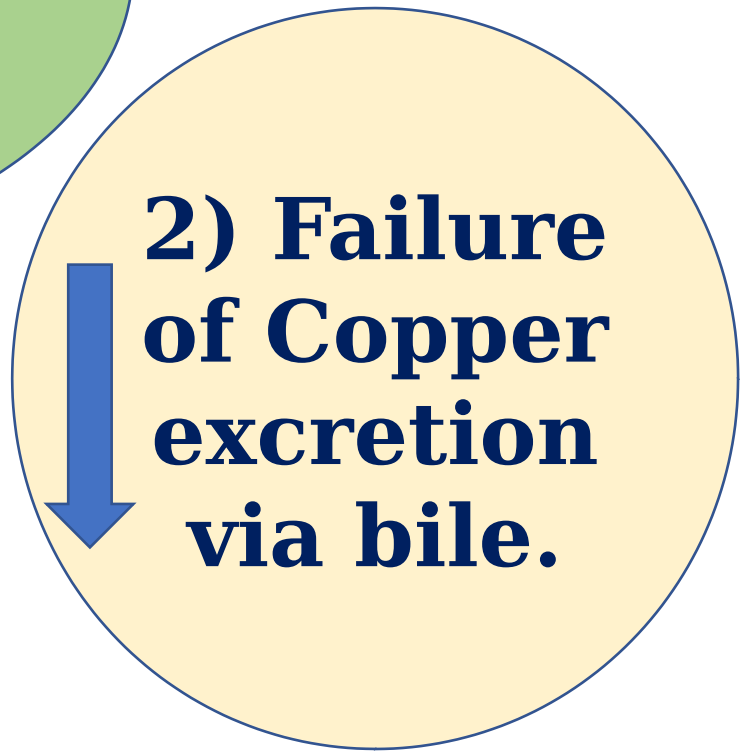
It is a genetic disease (autosomal recessive disorder), due to mutation of ATP7B gene encodending membrane bound copper transporting ATPase

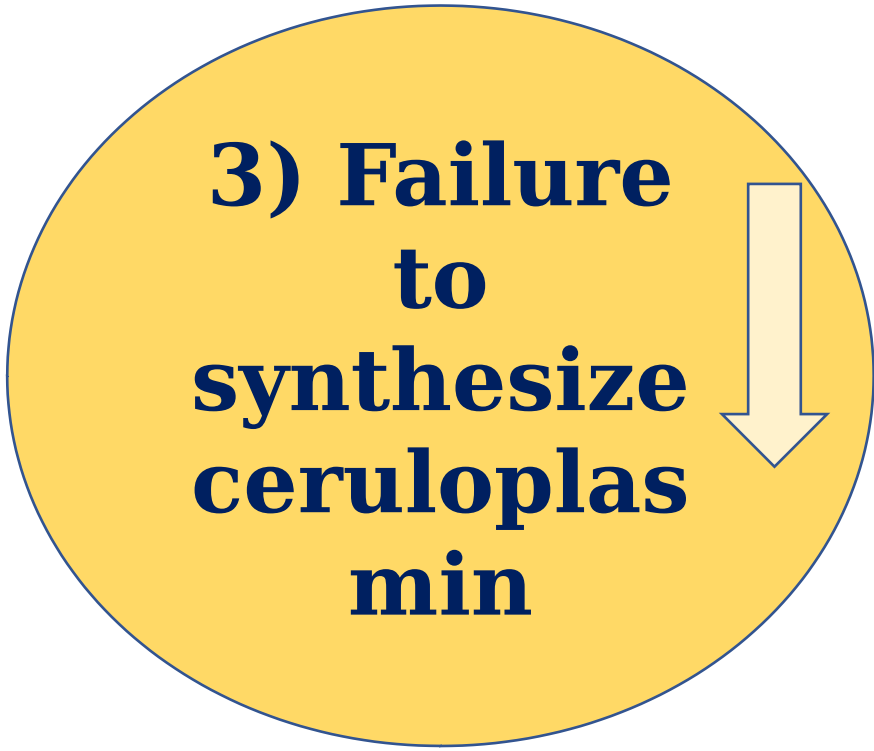
Cu absorption, transport and excretion in body



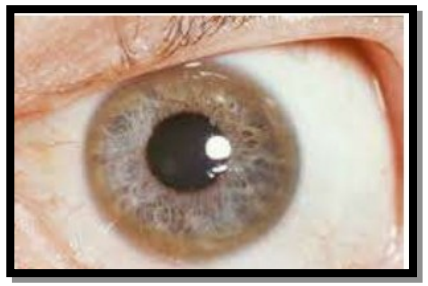
Biochemical basis of Wilson's:



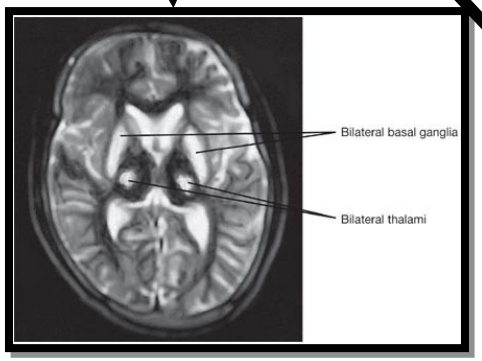




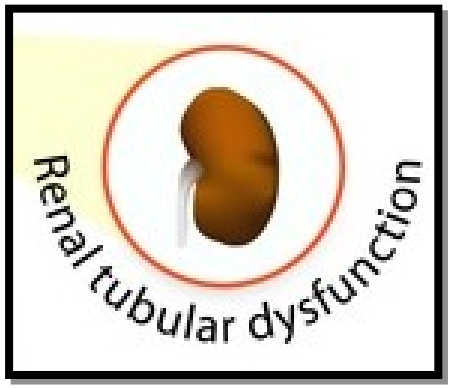
Tissues where excess Cu deposit

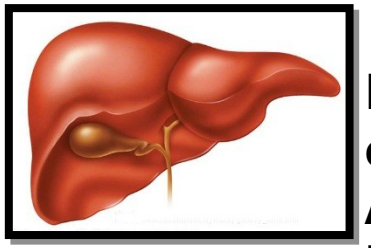


Dark, brown-colored rings around iris Cu deposit in (Descemet's membrane)



basal ganglia: Tremors, slurred speech change in behavior and Hyperintensities in MRI





Liver enlarged And may become cirrhotic

Laboratory diagnosis

Ceruloplasmin level< 20 mg/day
Urinary copper excretion rate >100mg/day
Free copper level > 3.9 ug/dl (N: 8-12ug/dl)
Liver biopsy : CU levels >250 mg of dry weight

What is the mechanism of action of penicillamine in the treatment of this condition?

- **chelates copper**
- **increase its excretion in urine.**

NB : Zinc can block intestinal absorption of cu

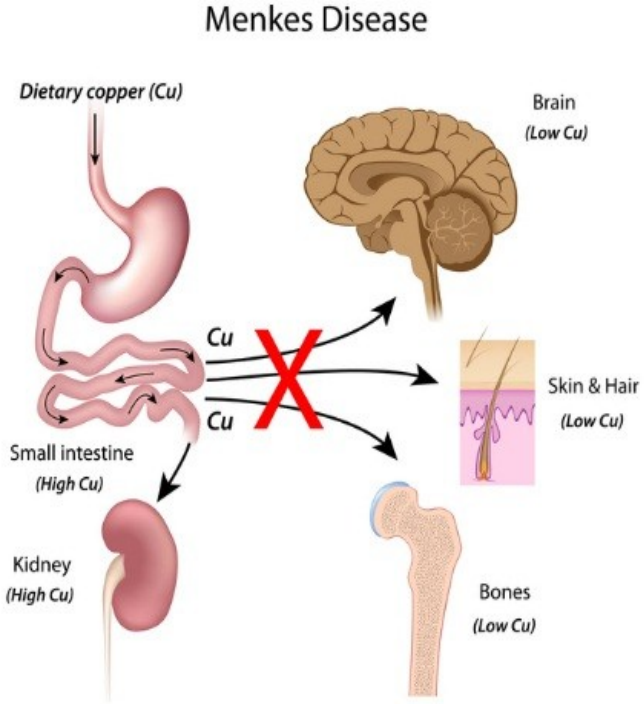
Hypocupremia:

mutation ATP7A
gene encoding for protein that is important for regulating Cu levels and distributions of copper in the body cells

ndrome (Menk's kinky hai

***Accumulation of Cu in intestine and kidney**

***Poor distribution of Cu in other body cells**

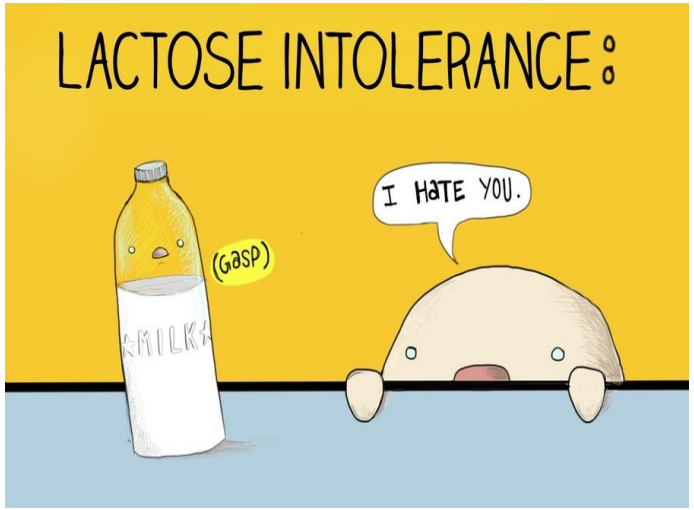


Case

- **A 25-year-old woman presents with a 10-year history of intermittent diarrhea, abdominal pain, and flatulence.**

- **Recently her symptoms have worsened. She said that the change in symptoms may be related to her increased intake of milk over the last few months.**
- **Abdominal examination reveals a slightly distended abdomen.**

What is your clinical impression?

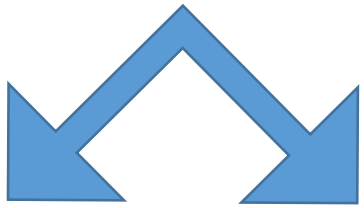


- Symptom:
- History
- Examination
- Bed test

- **Lactose intolerance due to Lactase deficiency**

Clinical significance of Digestion

- Lactose intolerance is the inability to digest lactose due to the deficiency of Lactase enzyme.
- Causes



Congenital

Acquired during lifetime

Primary

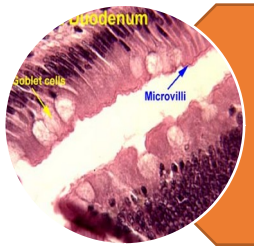
Secondary

Congenital Lactose intolerance

- **It is a congenital disorder**
- **There is complete absence or deficiency of lactase enzyme.**
- **The child develops intolerance to lactose immediately after birth.**
- **It is diagnosed in early infancy.**
- **Milk feed precipitates symptoms.**

Primary Lactase deficiency

- **Primary lactase deficiency develops over time**
- **There is no congenital absence of lactase but the deficiency is precipitated during adulthood.**
- **There is age-dependent loss of lactase activity affect lactase gene expression reduced amount of enzyme**
- **It is very common in Asian population.**
- **There is intolerance to milk + dairy products.**

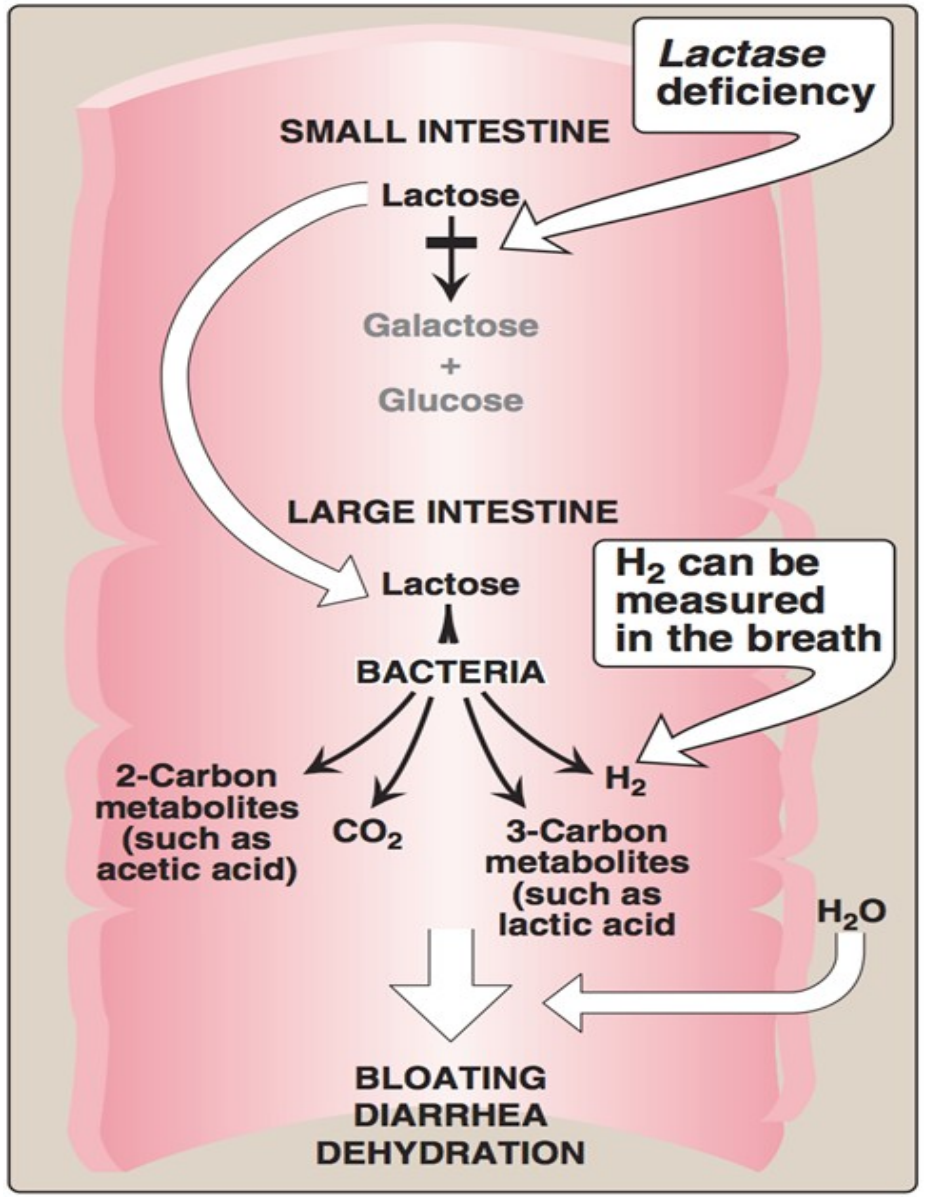


Secondary lactase deficiency

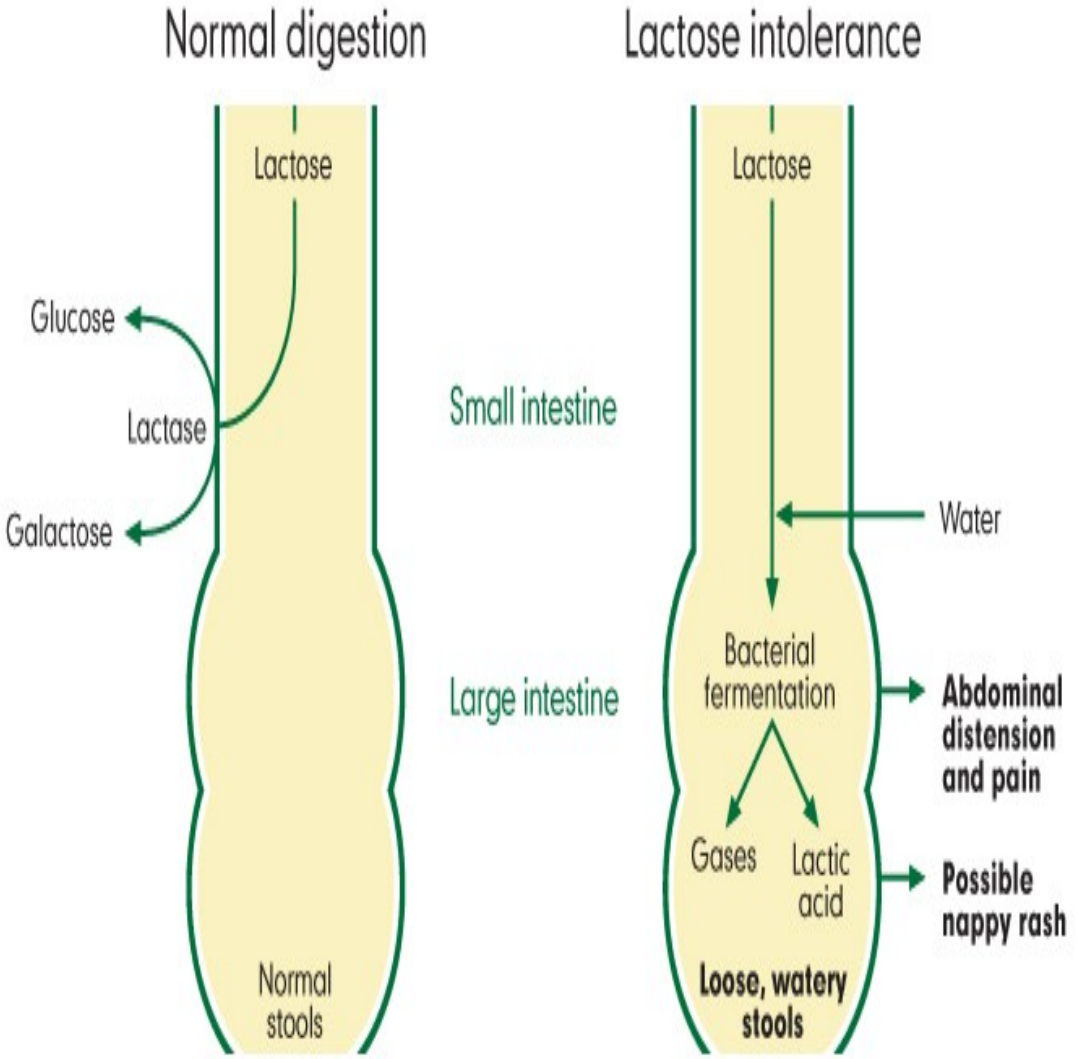
- This occurs because of mucosal damage or from medications resulting from certain **gastrointestinal diseases**, including exposure to **intestinal parasites** or **rotavirus.**

- Another form of temporary lactose intolerance is lactose overload is secondary to excess NSAID (non steroidal anti-inflammatory drug) use or **chemotherapy**.

Lactose intolerance



Symptoms of lactose intolerance



Biochemical basis of lactose intolerance

Lactose intolerance is a problem that results from an absence of lactase in the brush border of the small intestine.

Lactase is responsible for breaking down lactose into glucose and galactose, which are absorbed.

The undigested and unabsorbed lactose increases the osmotic gradient of the luminal contents, preventing the absorption of water.

The increased retention of fluid results in the symptoms of diarrhea with its abdominal distention and cramping.

The bacteria in the colon ferment the lactose into a variety of gases, leading to increased flatulence

Diagnosis

- *The commonly used tests are : -*
- **Hydrogen Breath Test**
- **Stool Acidity Test**
- **Mucosal biopsy** confirms the diagnosis.

Management of lactose intolerance

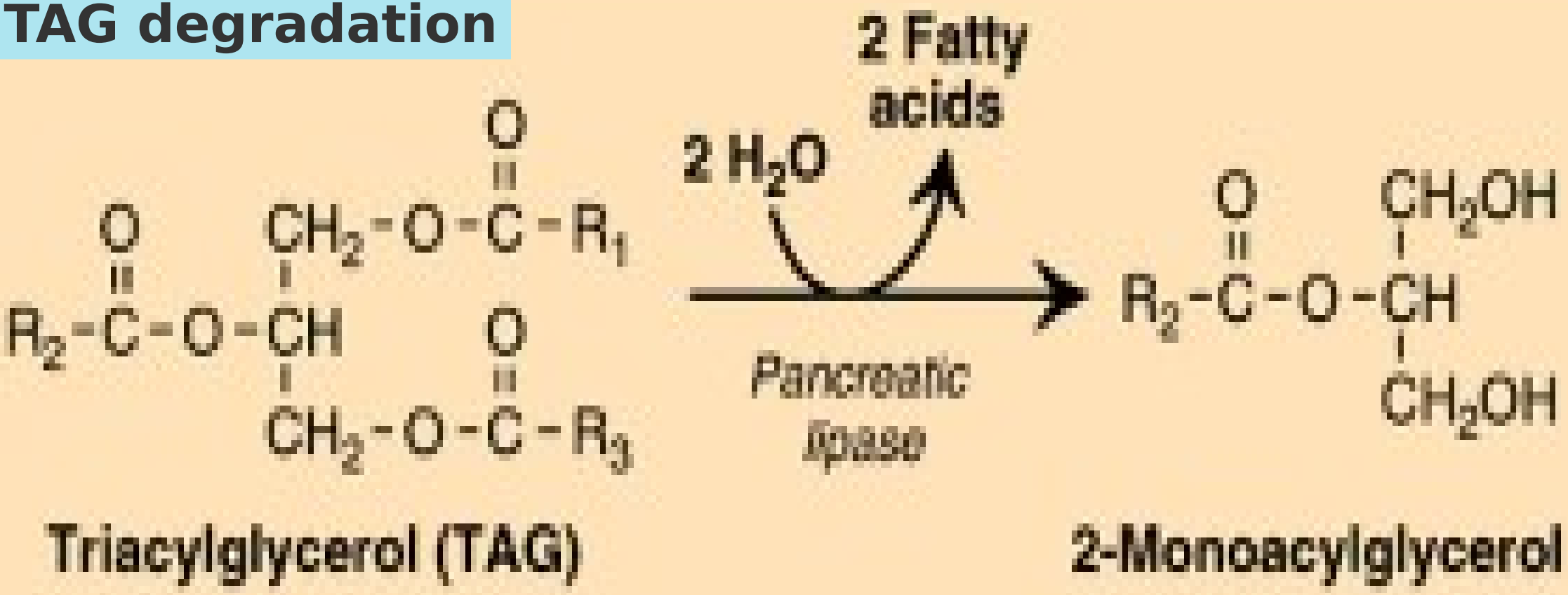
- Avoidance of dairy products.
- **Lactose-free, lactose-reduced milk**, Soy **milk** and other products may be recommended.
- **Lactase enzyme** drops or tablets(Yeast tablets) can also be consumed.
- Consume yogurts , some cheeses (**Bacterial action and processing decrease the lactose content)** ,
- Green vegetables (broccoli) (for Ca++ intake)

CASE

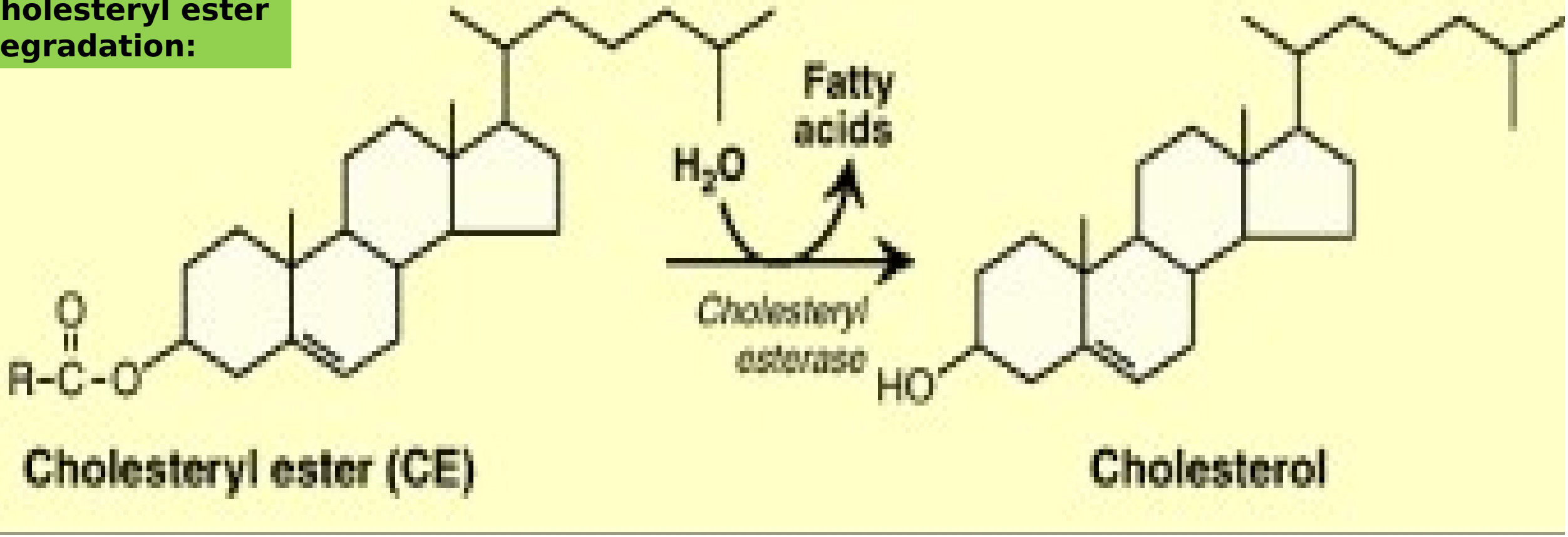
A 15 year old girl presents to the physician's office with a three year history of intermittent **diarrhea**.
She is thin and small for age but not cachectic. A stool examination is **negative for blood**. The 72-hour fecal fat study shows a **moderate increase in fat content**.
A CBC shows a mild anemia. Her iron studies indicate the presence of iron deficiency.
Her small size, the **steatorrhea and the iron deficiency all suggest the possibility of some type of GI malabsorption condition**.

List the pancreatic enzymes Used for Degradation of dietary lipids.

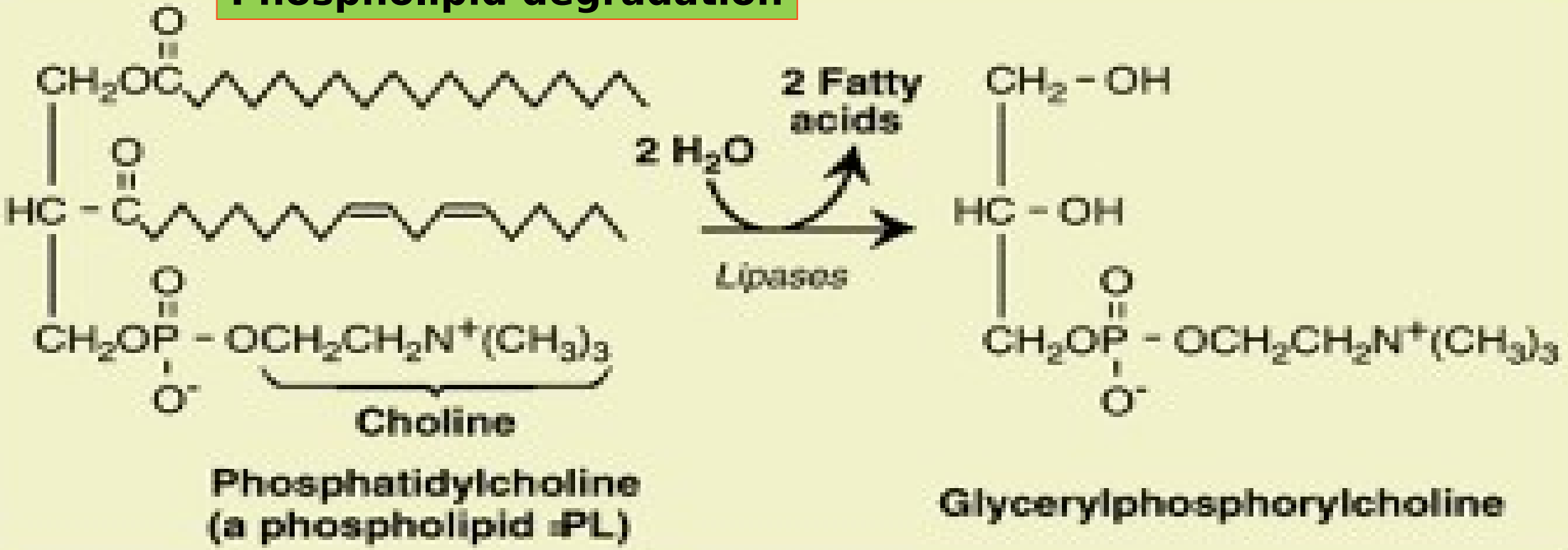
TAG degradation



Cholesteryl ester degradation:



Phospholipid degradation



Name the phases of protein digestion and discuss

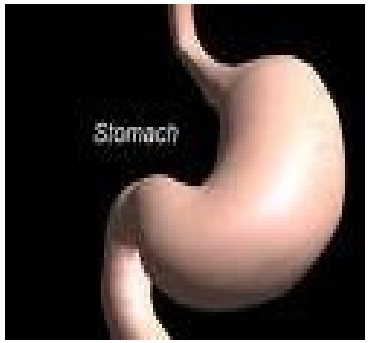
1. **Gastric phase**

- **2. Pancreatic phase**

- **3. Intestinal phase**

1-Gastric phase

: **Gastrin stimulates** release of **HCL** from **parietal cells**
pepsin from **chief cells**



Pepsin + HCL

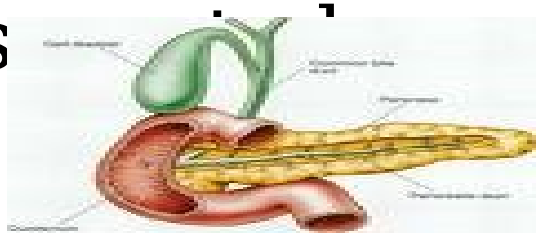
- **proteins**

smaller polypeptides + a.as

Pepsin is an endopeptidase, hydrolyses the peptide l
adjacent to acidic or aromatic amino acids.

2- Pancreatic phase

* The proteolytic action of pancreatic secretion is due to action of *endopeptidases* (which s[illegible] **zymogens)** and *carboxypeptidase.*



- **A) <u>Endopeptidases</u>** act in the **middle** of a polypeptide chain

Trypsinogen, chymotrypsinogen, proelastase

Trypsin, chymotrypsin, elastase

Polypeptides → **Tri/dipeptides + amino acids**

2- Pancreatic phase

1- Trypsin hydrolyses the peptide bonds containing the carboxylic group of basic amino acids (arginine).

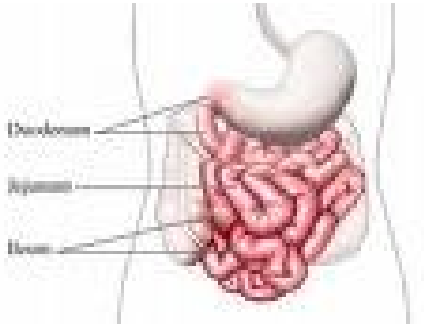
2- Chymotrypsin attacks the peptide bonds formed by **carboxylic group of aromatic amino acids, e.g. (phenyl alanine).**

3- Elastase hydrolyzes the peptide bonds next to some **non-polar amino acids** such as **(glycine & alanine).**

2- Pancreatic phase

- **B) Carboxy-peptidase**
- secreted as inactive pro-carboxypeptidase
- activated by trypsin.
- It acts on the **C-terminal peptide** bond.
- It is an **Exopeptidase.**

3- Intestinal phase



*Amino-peptidases

are **exopeptidases** separating

the **N - terminal amino acids** in oligopeptides.

*Tri-peptidases & Di-peptidases

act on tri- & dipeptides

producing **free amino acids**.

Case

- A 46 y-old woman presented for follow up examination. Her medical history is notable only for diabetes and borderline hypertension?? .She has a family history of Diabetes and HTN . The patient has not followed the recommended life style changes nor regular treatment . On Examination, her Bl.P 140/93 and her BMI is 35 kg/m2 . A fasting plasma glucose level is 250mg/dl .
- Lab date revealed
- AsT : 50Iu/ml (normal 10-40)
- ALT : 60 Iu/ml (normal 5-40)
  - TC = 362mg/dl TAG = 152 mg/dl
  - HDL = 36 mg/dl LDL = 266 mg/dl

- **What is most likely diagnosis ?**
- **What is the possible complication if not treated?**
- **What is the next step?**

What is most likely diagnosis ?

fatty liver

Causes of fatty liver

Metabolic

Nutritional

Drugs and toxins

The following mechanisms could be responsible for the occurrence of fatty liver:

1.↑ mobilization of FA (from diet or from adipose tissueas in starvation or DM) → elevated plasma FFA and their hepatic uptake →activated to acyl CoA =increased TAG synthesis.

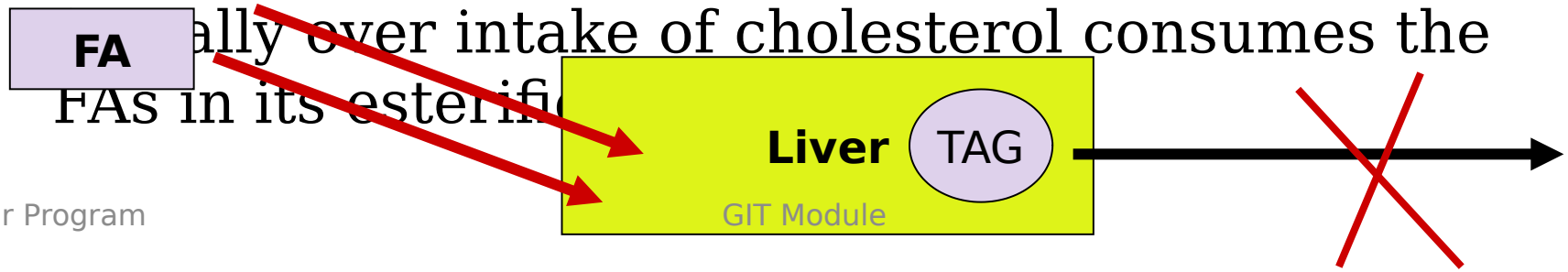
2. **Failure of liver to synthesize VLDL**, could be due to:

- failure to synthesize apoB100
- failure to release VLDL.
- failure to synthesize phospholipids due to :

✓ deficiency of lipotropic factors

✓ ↓ level of unsat FA that esterify position 2 of PL

ally over intake of cholesterol consumes the FAs in its esterifi



What is the possible complication if not treated?

The accumulated TAG results in liver enlargement , fibrosis and cirrhosis with impaired liver function

What is the next step?

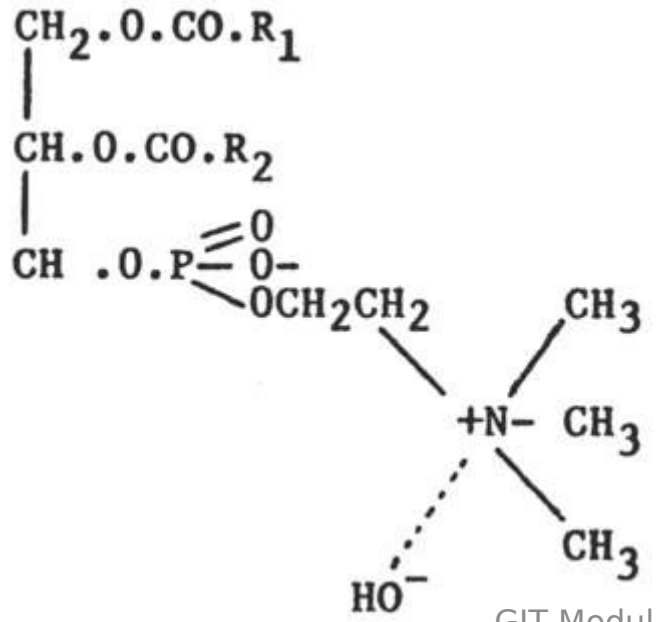
- **Follow the recommended life style changes (healthy diet with regular exercise)**
- **Regular treatment and controlled blood glucose level.**
- **Lipotropic factors**

Lipotropic Factors

- These are substances that protect against and cure fatty liver.
- They include mainly the substances **essential for synthesis of phospholipids** which are easily t iable to deposit

Lipotropic substances are:

1. **Choline, inositol, serine and ethanolamine** (constituents of PL)
2. **Methionine and betaine** (methyl donors for choline)
3. **Casein** (rich in methionine).



phosphatidyl choline

Lipotropic substances; con.

4. **Estrogen** inhibits HMG-CoA reductase (the key enzyme of FA synthesis).
5. **Essential FA**, eg, linoleic acid (Unsat.FA enter in PL synthesis)
6. **Vits. B12 , folic acid, pantothenic acid** (help transmethylation reactions for choline PL synthesis)
7. **Vit. E & selenium**: protect against FFA oxidation
8. **pyridoxine (B6)**: essential cofactors for enzymes involved in various metabolic


Thank you